PATENT
NY-HUBR 1230-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Chris RUNDFELD et al.	Group Art Unit: 1617
Application No.: 10/680,459	Examiner: D. R. CLAYTOR
Filed: October 6, 2003	Confirmation No.: 4494
For: USE OF DIHYDROIMIDAZOLONES FOR THE TREATMENT OF DOGS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF PROFESSOR WOLFGANG LÖSCHER UNDER 37 C.F.R. § 1.132

I, Prof. Dr. med. vet. Wolfgang Löscher, do hereby make the following declaration:

1. I am employed by the "Stiftung Tierärztliche Hochschule Hannover" (University of Veterinary Medicine, Hannover). I am Professor for Veterinary Pharmacology and Toxicology at the "Stiftung Tierärztliche Hochschule Hannover" and Chair of the Department of Pharmacology, Toxicology and Pharmacy of this University. I am also co-inventor of the subject patent application.

2. I have read and am familiar with the subject patent application. I am also familiar with the references cited by the Examiner during the prosecution of the patent

application including Bialer et al., Epilepsy Research 43 (2001), 11-58, which describes the activity of AWD 131-138 in animal seizure models, and the other cited references. As first and corresponding author of the reference "Evaluation of epileptic dogs as an animal model of human epilepsy", published in 1985 in Arzneimittelforschung / Drug Research vol. 35, pages 82-87, I am also familiar with the respective reference and with the body of literature dealing with epilepsy in dogs and epilepsy treatment in dogs.

3. I have read and am familiar with the arguments previously advanced by both the applicants and the Examiner concerning the use of AWD 131-138 for the treatment of idiopathic epilepsy in dogs.

4. The examiner cites from the above mentioned reference "Evaluation of epileptic dogs as an animal model of human epilepsy", that epilepsy in dogs closely approximates the disease in man (first paragraph of discussion). The examiner further cites that the epileptic dog is a suitable model for human epilepsy and that parallels were found between some of the antiepileptic drugs tested between effects in dogs and man.

5. While there are similarities between canine epilepsy and human epilepsy, *per se* this can not be generalized to the **treatment** of epilepsy. Furthermore, there are also many distinct differences between human epilepsy and canine epilepsy. One striking difference between human epilepsy and canine epilepsy relates to the seizure types which have been observed in man and not in dogs. A classification of human seizure types was established by the International League Against Epilepsy (ILAE).

According to this classification, idiopathic epilepsy in humans can be separated into two groups, i.e., (i) epilepsy with primary generalized seizures and (ii) epilepsy with partial or focal onset seizures. Primarily generalized seizures are further subdivided into (a) convulsive seizures, also called "grand mal seizure" and (b) epilepsy with absence type seizures, or so called "petit mal seizures" or absence epilepsy. Epileptic seizures with partial onset are further subdivided into complex partial seizures, i.e. (i) with impairment of consciousness, and (ii) simple partial seizures, i.e. without loss of consciousness during the seizure activity. Partial seizures may generalize resulting in generalized seizure activity. A brief summary of this classification is presented in table 1 of Licht et al (2002) **(Exhibit 1)**. The authors attempted to apply this classification of epilepsy used to characterize human epilepsy, to canine epilepsy. Based on a population of dogs with a large variety of seizures, they concluded that partial onset seizures was the most frequent seizure type in dogs, while primarily generalized seizures were less frequent (see table 2 of Licht et al, 2002). In the majority of animals, partial onset seizures led to generalized seizure activity at least time to time. Interestingly, none of the dogs examined exhibited absence type or "petit mal" seizures, but only convulsive seizures were observed. According to www.canine-epilepsy.net/basics/basics_index.html, absence or petit mal seizures differ from other seizures in that they probably represent a storm of inhibition rather than a storm of excitation within the brain. This creates a unique EEG pattern. This means that very different drugs are needed to treat petit mal seizures. According to this source, petit mal seizures do not occur in pets, supporting the observation made by Licht et al (2002) who did not report a single case of absence seizures in their experimental population.

6. This distinction between seizure types is important since animal models for human epilepsy are developed to model individual seizure types and not epilepsy as a whole. Therefore, activity of a test drug in a specific model supports activity of this drug only against the seizure type modelled. A typical example for an animal model developed to represent a specific human seizure type is the amygdala kindling model, which was developed to mimic complex partial seizures with secondary generalization. A different animal model is represented by the WAG rat model. WAG rats exhibit frequent petit mal or absence episodes which can be electrographically characterized and quantified. In WAG rats, the absence seizure episodes occur spontaneously every few minutes and no induction of seizure activity is needed to test a given test drug. Drugs which are effective in the amygdala kindling model may be active in human patients with partial onset seizures, while drugs with activity in the WAG rat model may be useful for the treatment of absence epilepsy in man., but one cannot conclude this with any certainty

7. The epileptic dog differs from standard animal models of epileptic seizures, including the standard, canine model of myoclonic seizures induced by timed intravenous infusion of pentylenetetrazole, or the DBA/2 mouse in one central point. In a standard model of epileptic seizures, the seizures are induced at a pre-determined time, while the drug to be tested can be administered at a time point selected by the researcher to allow for the highest possible plasma level of the drug at the time of the seizure. The epileptic dog, in contrast, is a model where the seizures may occur spontaneously at any time of the day, and at any day. The frequency of seizures in

dogs with epilepsy is well known to be below one seizure per day. Therefore, only drugs with kinetic behavior in dogs ensuring a chronic plasma (and brain) exposure with the active principle, if administered once daily or twice daily, can be tested in this model. Any drug with a short half life is not suitable to be tested in epileptic dogs since even with two to three administrations per day no constant and effective plasma (and brain) exposure with the active principle can be achieved. Due to the short half life and the rapid elimination of the drug the plasma level may fall below the active plasma level between administrations.

8. In table 3 of our publication entitled "Evaluation of epileptic dogs as an animal model of human epilepsy" the kinetic behaviour in dogs and in humans of most antiepileptic drugs which were marketed before 1985 were listed to allow comparison between dogs and humans. Interestingly, most antiepileptic drugs had a very short half life in dogs while the half life in man was much longer. Only phenobarbital and primidone, i.e. the two drugs which are commonly used for the treatment of epilepsy in dogs, had a sufficiently long half life to allow for treatment of dogs. The other two drugs with acceptable half life, i.e. ethosuximide and trimethadione, are agents which are only useful for the treatment of specific types of human epilepsy, i.e. absence epilepsies, also called petit mal epilepsies, which are not associated with convulsions. This type of epilepsy is not seen in dogs. As can be seen from table 3 and from the text, agents which were used as "first line" drugs for the treatment of human epilepsy at the time when this study was published, i.e. phenytoin, carbamazepine, valproic acid, diazepam, clonazepam and nitrazepam, have a very short half life in dogs. In fact, we state also in

our paper, that this short half life is even further shortened due to induction of microsomal liver enzymes resulting in even faster metabolism of the drugs in dogs. Studies in healthy dogs have shown that, even with high daily doses, effective plasma levels cannot be maintained. Therefore, we were only able to select from primidone and phenobarbital as test drugs and we selected primidone. While we were able to show that the drug, which is commonly used to treat epilepsy in dogs and which is known to have clinical efficacy in man, was effective in a setting of a clinical study in dogs, we concluded and continue to conclude that the epileptic dog is only a model of human epilepsy (i) if the pharmacokinetics of the agent in question is similar between dogs and humans and (ii) if the kinetics are suitable to allow for chronic exposure of the dog during chronic treatment. We state in the publication (page 86, right column, 2nd paragraph): "Consequently, the short half lives of a number of other antiepileptic drugs in dogs limit the usefulness of the epileptic dog as a model for antiepileptic drug evaluation. In fact, the preliminary data on chronic treatment with valproic acid, phenytoin and carbamazepine indicate that these major antiepileptic drugs are not effective in the dog model."

9. This difference between of the epileptic dog and the human patient suffering from epilepsy has prevented the use of the epileptic dog as a standard model for testing of novel anticonvulsants. Indeed, no prospective study has been published where the epileptic dog was used as a model of human epilepsy, so as to test the activity of a novel drug in development. Our attempt to position the epileptic dog as an interesting model of human epilepsy has therefore failed, for all of the reasons set forth

in this declaration. Dogs have a high metabolizing capacity, which leads to short half lives of many drugs. This metabolizing capacity is even further strengthened upon repeated administration of many medications, since induction of metabolizing enzymes results in an even lower achievable plasma level and an even shorter half life. A more recent example of these characteristics, i.e. the short half life and the enzyme induction, is described in Schicht et al., Pharmacokinetics of oxcarbazepine in the dog, J Vet Pharmacol Ther. 1996;19:27-31 (**Exhibit 2**). The novel anticonvulsant oxcarbazepine, which is marketed for treatment of human epilepsy, was tested in dogs. The initial half life of this drug was only 4 hours, upon repeated administration, (i.e., three times a day, to 1-2 hours within 3 days rendering the drug useless for treatment of dogs. The authors conclude that oxcarbazepine as compared to carbamazepine, offers no advantage for the treatment of epileptic dogs since due to this short half life, no chronic exposure can be achieved, as has been observed previously for carbamazepine.

10. In conclusion, while epilepsy with convulsive seizures in dogs closely approximates the disease in man, this can not be extrapolated to treatment. The dog is not a suitable model for human epilepsy and results for drugs tested in humans are not extrapolatable to canine idiopathic epilepsy. The specific characteristics of canine drug metabolism and kinetics, data generated in models with induced seizures such as the DBA/2 mouse of the timed intravenous infusion of pentylenetetrazol in dogs or in other species and even data generated in human patients suffering from epilepsy are not sufficient to identify a successful antiepileptic drug for the treatment of canine idiopathic epilepsy. This is true for drugs which are already available for human idiopathic

epilepsy, as well as for any new chemical entity which has only been tested in individual seizure models, which represent models of induced seizures.

11. I hereby declare that all statements made herein where done on the basis of my best knowledge and that all statements made are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: March 16, 2010

By: _____
Prof. Wolfgang Löscher

Curriculum Vitae

BIOGRAPHICAL SKETCH

Wolfgang Löscher

Wolfgang Löscher is Professor and Director of the Department of Pharmacology, Toxicology and Pharmacy at the University of Veterinary Medicine Hannover, as well as Head of the Center for Systems Neuroscience in Hannover, Germany. He was born in Berlin, Germany, in 1949, and graduated from the Free University of Berlin in 1974 with a degree in Veterinary Medicine. He pursued postgraduate training and specialization in Pharmacology, particularly Neuropharmacology, and Toxicology in Germany, Denmark, and the United States and holds board certifications in these specialties. He has held posts in academical institutions and pharmaceutical industry and was appointed to the Department of Pharmacology in Hannover in 1987. His research interests are in the pharmacology of the brain, including the pharmacology of antiepileptic drugs, the mechanisms of pharmacoresistant epilepsy, and the pathophysiology of temporal lobe epilepsy with the aim to find new targets for treatment. His many cooperations with pharmaceutical industry have fostered the development of new antiepileptic drugs such as levetiracetam. In addition, his research efforts have included the investigation of tolerance and dependence of psychoactive drugs, the pharmacology and pathophysiology of rodent models of movement disorders such as dystonia, as well as evaluation and characterization of toxic effects of electromagnetic fields. He was a founding editor of the journal Epilepsy Research and serves on the editorial board of several scientific journals, including Epilepsia. He has over 400 refereed publications

and is listed in the 2008 ISI web-list of the world's most cited authors. He has obtained several awards for this research, including the Epilepsy Research Award for Outstanding Contributions to the Pharmacology of Antiepileptic Drugs of the International League against Epilepsy in 2001 and the American Epilepsy Society's Epilepsy Research Award for Basic Science Research in 2006.

Selected Publications

In the years between 1976 until 2009, I have published numerous articles dealing with dealing with epilepsy, anticonvulsant drugs and development of anticonvulsant or antiepileptic agents. Medline lists 294 articles using the search terms "Löscher" and "Epilepsy", including 42 review articles.

These review articles are listed below:

1: Löscher W. Preclinical assessment of proconvulsant drug activity and its relevance for predicting adverse events in humans. Eur J Pharmacol. 2009 May 21;610(1-3):1-11.

2: Löscher W, Cole AJ, McLean MJ. Commentary: physical approaches for the treatment of epilepsy: electrical and magnetic stimulation and cooling. Neurotherapeutics. 2009 Apr;6(2):258-62.

3: Löscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia. 2009 Jan;50(1):1-23.

4: Löscher W, Gernert M, Heinemann U. Cell and gene therapies in epilepsy--promising avenues or blind alleys? Trends Neurosci. 2008 Feb;31(2):62-73.

5: Löscher W. The pharmacokinetics of antiepileptic drugs in rats: consequences for maintaining effective drug levels during prolonged drug administration in rat models of epilepsy. Epilepsia. 2007 Jul;48(7):1245-58.

6: Löscher W. Mechanisms of drug resistance in status epilepticus. Epilepsia. 2007;48 Suppl 8:74-7. Erratum in: Epilepsia. 2007 Dec;48(12):2384.

7: Löscher W. Drug transporters in the epileptic brain. Epilepsia. 2007;48 Suppl 1:8-13.

8: Löscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. Epilepsia. 2006 Aug;47(8):1253-84.

9: Stefan H, Lopes da Silva FH, Löscher W, Schmidt D, Perucca E, Brodie MJ, Boon PA, Theodore WH, Moshé SL. Epileptogenesis and rational therapeutic strategies. Acta Neurol Scand. 2006 Mar;113(3):139-55.

10: W, Poulter MO, Padjen AL. Major targets and mechanisms of antiepileptic drugs and major reasons for failure. Adv Neurol. 2006;97:417-27.

11: Löscher W. Mechanisms of drug resistance. Epileptic Disord. 2005 Sep;7 Suppl 1:S3-9. Review. Erratum in: Epileptic Disord. 2008 Jun;10(2):191.

12: Löscher W, Potschka H. Drug resistance in brain diseases and the role of drug efflux transporters. Nat Rev Neurosci. 2005 Aug;6(8):591-602.

13: Schmidt D, Löscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. Epilepsia. 2005 Jun;46(6):858-77.

14: Schmidt D, Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. Acta Neurol Scand. 2005 May;111(5):291-300.

15: Löscher W, Potschka H. Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. Prog Neurobiol. 2005 May;76(1):22-76.

16: Löscher W, Potschka H. Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. NeuroRx. 2005 Jan;2(1):86-98.

17: Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat Med. 2004 Jul;10(7):685-92.

18: Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. Nat Rev Neurosci. 2004 Jul;5(7):553-64.

19: Schmidt D, Baumgartner C, Löscher W. Seizure recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: a review of current clinical experience. Epilepsia. 2004 Feb;45(2):179-86.

20: Schmidt D, Löscher W. How effective is surgery to cure seizures in drug-resistant temporal lobe epilepsy? Epilepsy Res. 2003 Oct;56(2-3):85-91.

21: Stables JP, Bertram EH, White HS, Coulter DA, Dichter MA, Jacobs MP, Loscher W, Lowenstein DH, Moshe SL, Noebels JL, Davis M. Models for epilepsy and epileptogenesis: report from the NIH workshop, Bethesda, Maryland. Epilepsia. 2002 Nov;43(11):1410-20.

22: Löscher W. Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and post-status epilepticus models of temporal lobe epilepsy. Epilepsy Res. 2002 Jun;50(1-2):105-23.

23: Löscher W, Schmidt D. New horizons in the development of antiepileptic drugs. Epilepsy Res. 2002 Jun;50(1-2):3-16.

24: Coulter DA, McIntyre DC, Löscher W. Animal models of limbic epilepsies: what can they tell us? Brain Pathol. 2002 Apr;12(2):240-56.

25: Löscher W, Potschka H. Role of multidrug transporters in pharmacoresistance to antiepileptic drugs. J Pharmacol Exp Ther. 2002 Apr;301(1):7-14.

26: Löscher W. Current status and future directions in the pharmacotherapy of epilepsy. Trends Pharmacol Sci. 2002 Mar;23(3):113-8.

27: Löscher W. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. CNS Drugs. 2002;16(10):669-94.

28: Löscher W. Animal models of drug-resistant epilepsy. Novartis Found Symp. 2002;243:149-59; discussion 159-66, 180-5.

29: Löscher W. Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. Prog Neurobiol. 1999 May;58(1):31-59.

30: Trinka E, Moroder T, Nagler M, Staffen W, Löscher W, Ladurner G. Clinical and EEG findings in complex partial status epilepticus with tiagabine. Seizure. 1999 Feb;8(1):41-4.

31: Löscher W. Pharmacology of glutamate receptor antagonists in the kindling model of epilepsy. Prog Neurobiol. 1998 Apr;54(6):721-41.

32: Löscher W. New visions in the pharmacology of anticonvulsion. Eur J Pharmacol. 1998 Jan 19;342(1):1-13.

33: Löscher W. Animal models of intractable epilepsy. Prog Neurobiol. 1997 Oct;53(2):239-58. Review. PubMed PMID: 9364612.

34: Löscher W, Ebert U. The role of the piriform cortex in kindling. Prog Neurobiol. 1996 Dec;50(5-6):427-81. Review. PubMed PMID: 9015822.

35: Löscher W, Wauquier A. Use of animal models in developing guiding principles for polypharmacy in epilepsy. Epilepsy Res Suppl. 1996;11:61-5.

36: Löscher W, Ebert U. Basic mechanisms of seizure propagation: targets for rational drug design and rational polypharmacy. Epilepsy Res Suppl. 1996;11:17-43.

37: Löscher W. Basic aspects of epilepsy. Curr Opin Neurol Neurosurg. 1993 Apr;6(2):223-32.

38: Löscher W. Pharmacological, toxicological and neurochemical effects of delta 2(E)-valproate in animals. Pharm Weekbl Sci. 1992 Jun 19;14(3A):139-43.

39: Löscher W, Schmidt D. Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. Epilepsy Res. 1988 May-Jun;2(3):145-81.

40: Frey HH, Löscher W. Pharmacokinetics of anti-epileptic drugs in the dog: a review. J Vet Pharmacol Ther. 1985 Sep;8(3):219-33.

41: Löscher W. Genetic animal models of epilepsy as a unique resource for the evaluation of anticonvulsant drugs. A review. Methods Find Exp Clin Pharmacol. 1984 Sep;6(9):531-47.

42: Löscher W, Meldrum BS. Evaluation of anticonvulsant drugs in genetic animal models of epilepsy. Fed Proc. 1984 Feb;43(2):276-84.